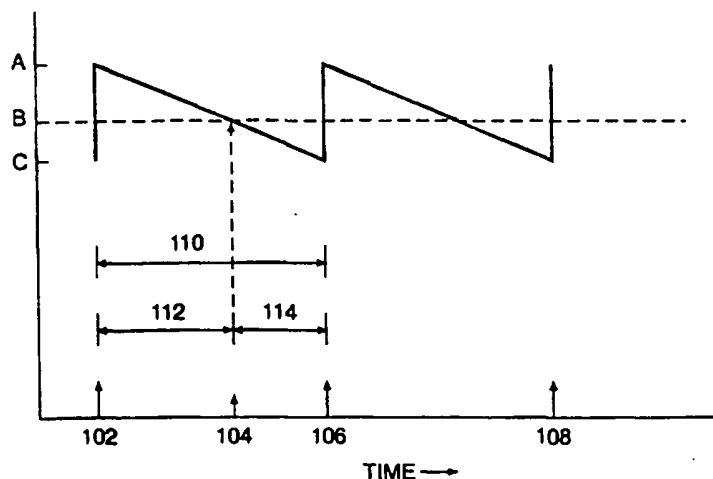




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61N 1/368	A1	(11) International Publication Number: WO 99/61101 (43) International Publication Date: 2 December 1999 (02.12.99)
(21) International Application Number: PCT/US99/11375 (22) International Filing Date: 21 May 1999 (21.05.99) (30) Priority Data: 09/084,571 26 May 1998 (26.05.98) US (71)(72) Applicant and Inventor: MOWER, Morton, M. [US/US]; 3908 N. Charles Street #1001, Baltimore, MD 21218 (US). (74) Agents: ROBERTS, Jon, L. et al.; Roberts & Abokhair, LLC, Suite 1000, 11800 Sunrise Valley Drive, Reston, VA 20191-5403 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	

(54) Title: METHOD ALLOWING CYCLIC PACING WITH AVERAGE RATE JUST ABOVE THE INTRINSIC RATE



(57) Abstract

Method and apparatus for cyclic ventricular pacing starting at a rate just above the intrinsic atrial firing rate (overdrive pacing), followed by relaxation to a rate just below the intrinsic atrial firing rate (ventricular escape). The method and apparatus can be applied to one or both ventricles, and can utilize one or more electrodes per ventricle. The electrode(s) can be applied to inner or outer ventricular surfaces. Relaxation protocols as a function of time can be linear, curvilinear to include exponential, or mixtures thereof. Furthermore, relaxation protocols can include one or more periods of time during which the pacing rate is held constant. Typically, the average ventricular pacing rate using this invention will be slightly greater than the intrinsic atrial firing rate, though alternate embodiments that encompass average ventricular pacing rates that are equal to or slightly less than the intrinsic atrial firing rate are also envisioned. Application of this method and apparatus to a heart in need thereof will produce a heart with an optimally minimized energy output requirement.

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1 METHOD ALLOWING CYCLIC PACING WITH AVERAGE RATE JUST ABOVE THE INTRINSIC RATE
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5 **Field of the Invention**

6 The present invention relates generally to pacemakers to control the beating of hearts.
7 In particular, the present invention relates to pacemakers used to promote, on a cyclic basis,
8 ventricular tracking of atrial firing by overdriving ventricular pacing at a rate slightly over the
9 intrinsic heart (atrial) rate, followed by gradual relaxation of the rate of ventricular
10 stimulation to the point of decoupling of ventricular beating from atrial firing, especially in
11 conjunction with ventricular synchronizing techniques such as biventricular pacing, biphasic
12 pulsing, and/or multiple-site ventricular pacing.

13 **Background of the Invention**

14 A-V blocks, encountered frequently in cardiac patients, arise when electrical impulses
15 flowing from the SA node along the conduction bundles are delayed when they reach the A-V
16 junction/A-V node. In some pathologies, if an A-V delay is sufficiently great, the ventricles
17 will beat at their own intrinsic and slower rate. With A-V blocks in other pathologies, the
18 ventricles can beat at a variable and/or intermittent rate, or ectopic foci can appear, potentially
19 leading to life threatening ventricular fibrillation.

20 A variety of strategies have been employed for pacemakers to overcome the adverse
21 physiological effects of A-V blocks. One such strategy is overdriving or overpacing, in
22 which the pacemaker stimulates the ventricles at a faster rate than the atrial beating rate. A
23 problem encountered with such strategies is that the atrial and ventricular beating can not be
24 coordinated for optimal pumping efficiency. Another problem is that such fast ventricular
25 pacing rates fatigue the heart because physiological and biochemical functioning generally are
26 not optimized. Furthermore, such additional fatigue only imposes greater restraints on the
27 already limited life style of the typical cardiac patient. Thus, the patient with an already
28 weakened heart can be subjected to unnecessary overstimulation, and be stressed and further
29 weakened as a result of application of current pacemaking protocols.

1 Patented technologies relating to overdriving pacing with subsequent relaxation of the
2 pacing rate include U.S. Patent No. 5,626,620 to Kieval, et al., which discloses a pacemaker
3 stimulation protocol in which fusion and/or near fusion beats are detected by monitoring
4 changes in the characteristics of the evoked QRS. The protocol is adjustable to allow
5 selection of an acceptable percentage of fusion beats. When an unacceptable fusion
6 percentage is measured, the A-V delay is automatically decreased to lead to a higher
7 ventricular beating rate from the pacemaker's synchronous pace pulses (ventricular
8 "capture"). Once ventricular capture is maintained for a predetermined time interval or
9 number of cycles without an unacceptable rate of fusion, the A-V interval is incrementally
10 increased to produce a beating rate toward the rate at which fusion had previously occurred.
11 Upon again meeting an unacceptable fusion percentage, the A-V delay is automatically
12 decreased, and the cycle continues so as to approximate the longest A-V interval (i.e., the
13 slowest ventricular beating rate) consistent with avoiding fusion.

14 U.S. Patent No. 5,527,347 to Shelton, et al. discloses a pacemaker ventricular
15 stimulation protocol in which the A-V delay is slowly increased until fusion occurs, at which
16 point the A-V delay is decreased slightly. The cycle is then repeated. Thus, the A-V delay is
17 cyclically maintained in a small range of about that corresponding to fusion, to slightly lower
18 values (i.e., higher ventricular beating rate).

19 U.S. Patent No. 5,522,858 to van der Veen discloses a pacemaker stimulation protocol
20 in which A-V delays are gradually decreased until ventricular tracking of atrial firing occurs.
21 In particular, the ventricles are stimulated after the atrial depolarization impulse reaches the
22 ventricles, but are not stimulated during the ventricular refractory period. The net effect is to
23 decrease the prolonged A-V delay period, and thus increase the ventricular beating rate. In
24 small increments, the A-V delay period then is further decreased until ventricular tracking is
25 observed.

26 U.S. Patent No. 5,480,413 to Greenhut, et al. discloses a means for using a pacemaker
27 to correct ventricular beating rate instability in the presence of atrial
28 fibrillation/tachyarrhythmia. First, ventricular beating is decoupled from atrial beating by
29 gradually increasing the ventricular beating rate (dual or multichamber pacemakers are
30 switched to a single chamber pacing mode) via appropriately spaced electrical stimulations.
31 Once a stabilized beating rate is achieved at the higher ventricular beating rate, then the rate

1 of ventricular stimulation is slowly decreased to the lowest rate that provides ventricular rate
2 stability, and held at this rate until the atrial tachyarrhythmia/fibrillation disappears. Dual or
3 multi-chamber (atria and ventricles) pacemaking is then resumed.

4 U.S. Patent No. 5,441,522 to Schüller discloses a dual chamber pacemaker
5 stimulation protocol in which the A-V interval is cycled between two values when retrograde
6 conduction from ventricular stimulation renders the atria refractory to the normally timed
7 stimulation by the pacemaker. When such a condition is sensed, the A-V interval is
8 shortened to one value. Once a predetermined time or number of pulses has occurred, or once
9 a spontaneous ventricular reaction is sensed within the shortened A-V interval, then the
10 longer A-V interval is restored.

11 U.S. Patent No. 5,340,361 to Sholder discloses a ventricular stimulation protocol in
12 which the A-V interval is automatically adjusted to just less than that for the intrinsic (and
13 pathological) rhythm to produce a ventricular firing that is slightly in advance of the intrinsic
14 ventricular firing time. This invention overcomes the problem of abnormal A-V delay, which
15 decreases cardiac efficiency due to non-optimal atrial-ventricular synchronization. The rates
16 of atrial firing and ventricular firing are equal in this invention.

17 U.S. Patent No. 5,334,220 to Sholder discloses a ventricular stimulation protocol in
18 which the A-V interval is automatically adjusted to avoid ventricular stimulation at a time
19 that would result in fusion (at the cross-over point) with the endogenous ventricular
20 stimulation. A final A-V value is selected by incrementally adjusting the A-V interval until
21 the crossover point is reached with respect to the R wave. The final A-V value that is set is
22 based on the determined cross-over point, adjusted by a small margin. Thus, this procedure
23 overdrives the intrinsic rhythm to ensure a suitably short A-V interval/delay that, otherwise,
24 would impair cardiac pumping efficiency. When this procedure is invoked (automatically)
25 too frequently, it is suspended for a predetermined period.

26 U.S. Patent No. 5,105,810 to Collins, et al. discloses a cyclic protocol for achieving
27 the minimum voltage for ventricular pacing for the purpose of extending the life of batteries
28 used in pacemakers. The protocol uses a series of bradycardia support pacing pulses at a
29 predetermined voltage, and ventricular pressure measurements are analyzed during the pulse
30 train to determine if capture has occurred. If capture has occurred during the pulse train,
31 bradycardia support pacing pulses again are delivered once the stimulus voltage has been

1 decreased by a step. If capture is the result, then the decremental voltage stepping and
2 capture assessing is continued until capture is lost, at which point the voltage is incrementally
3 increased until capture occurs.

4 U.S. Patent No. 4,503,857 to Boute, et al. discloses a ventricular pacing protocol in
5 which either spontaneous bradycardia or tachycardia is altered first by ventricular capture,
6 followed by gradual increase or decrease, respectively, in the rate of pulse pacing until a
7 normal programmed pacing rate is reached.

8 As can be seen from earlier inventions, pacemakers utilize overdrive ventricular
9 pacing that adjusts the A-V interval/delay in a manner that avoids fusion, and that controls
10 ventricular firing solely by the imposed pacing impulses. However, such protocols have not
11 been optimally designed to minimize the energy expenditure of the already compromised
12 patient's heart. Generally, the above references are designed to change the stimulation rate by
13 adjustment of the A-V interval/delay in order to achieve a predetermined rate or a
14 physiological standard.

15 What is needed is a pacemaker with a ventricular firing protocol that minimizes the
16 energy of the heart used for contraction/pumping work. Furthermore, what is needed is a
17 pacemaker with a ventricular firing protocol in which the maximum overdrive pacing rate is
18 only slightly (i.e., only a few beats per minute — ideally two or three beats per minute)
19 greater than the atrial firing rate at the commencement of the first cycle of the protocol. In
20 addition, what is needed is a pacemaker for ventricular firing that uses a pacing protocol that
21 achieves re-synchronization/fusion, so as to produce the least amount of stress on a heart
22 which may already be in a weakened condition.

23 Lastly, an improved means for stimulating muscle tissue, wherein the contraction
24 elicited is enhanced and the damage to the tissue adjacent to the electrode is diminished, is
25 also desired.

26 Enhanced myocardial function is obtained through the biphasic pacing of the present
27 invention. The combination of cathodal with anodal pulses of either a stimulating or
28 conditioning nature, preserves the improved conduction and contractility of anodal pacing
29 while eliminating the drawback of increased stimulation threshold. The result is a
30 depolarization wave of increased propagation speed. This increased propagation speed
31 results in superior cardiac contraction leading to an improvement in blood flow. Improved

1 stimulation at a lower voltage level also results in reduction in power consumption and
2 increased life for pacemaker batteries.

3 4 **Summary of the Invention**

5 It is therefore an object of the present invention to provide a pacemaker with a
6 ventricular firing protocol that minimizes the energy required for contraction and pumping of
7 the heart of a cardiac patient.

8 It is another object of the present invention to provide a pacemaker with a ventricular
9 firing protocol that uses ventricular overdrive pacing only to a minimal degree; i.e., overdrive
10 pacing is just a few beats per minute greater than the intrinsic atrial firing rate.

11 It is a further object of the present invention to provide a pacemaker with a ventricular
12 firing protocol with a pacing relaxation period in which the ventricular pacing rate is slowly
13 decreased to just slightly less (i.e., by only 1-2 beats per minute) than the intrinsic atrial firing
14 rate before commencement of the next cycle.

15 It is a further object of the present invention to directly adjust the ventricular pacing
16 cycle length, rather than the A-V delay.

17 It is a further object of the present invention to provide rate modulation in conjunction
18 with multiple-site ventricular pacing.

19 The present invention accomplishes the above objectives by providing a ventricular
20 firing protocol that is initiated by synchronization with the QRS complex of the
21 electrocardiogram. The time from one QRS complex to the next constitutes a practical
22 definition of the length of a heart beat, thereby providing the control circuit with a ready,
23 strong reference point that serves as a timing mark for the timing of the firing trigger of the
24 first electrical impulse to the ventricle(s). In theory, a P wave with an appropriate time
25 interval could work. However, the weak P wave could disappear in the presence of
26 conditions such as atrial fibrillation. This is particularly true in the case of pathological
27 hearts. Therefore, the QRS complex, because of its large amplitude, serves as the best
28 reference point available in the electrocardiogram. However, it is to be understood that the
29 practice of the initial phase of this invention amounts to indirect timing/coordination with
30 respect to atrial firing and contraction, as this is required for optimal total cardiac functioning.

31 The ventricular firing protocol is activated upon detection of a QRS complex, and is

1 set at an overdrive rate of only a few beats per minute (i.e., no more than 3-5 beats per
2 minute) greater than the intrinsic atrial firing rate. Next, the ventricular firing rate is slowly
3 decreased ("relaxed") to a rate just a few beats per minute (i.e., no more than 2-3 beats per
4 minute; ideally, only 1-2 beats per minute) below the intrinsic atrial firing rate, which leads to
5 ventricular escape (i.e., atrial firing and contraction no longer coordinate perfectly with
6 ventricular firing and contraction).

7 Subsequently, a new cycle is commenced.

8 Thus, the present invention uses a stimulation rate that is continuously cycled from a
9 highest rate that is just barely above the intrinsic atrial firing rate, to a rate just barely below
10 the intrinsic atrial firing rate. Such a stimulation protocol is expected *a priori* to provide a
11 good approximation of an optimal lowest energy requiring protocol. Therefore, the limited
12 energy of the cardiac patient can be used wisely and optimally to the benefit of the already
13 compromised patient. In summary, this technique allows pacing at an average rate that is just
14 above the intrinsic heart rate so as to maximize inotropic pacing effects at minimal heart
15 rates, and thereby conserve the precious energy of the patient's heart.

16 Additionally, the ventricular firing protocol of the present invention can be used in
17 conjunction with biphasic pacing. The method and apparatus relating to biphasic pacing
18 comprises a first and second stimulation phase, with each stimulation phase having a polarity,
19 amplitude, shape, and duration. In a preferred embodiment, the first and second phases have
20 differing polarities. In one alternative embodiment, the two phases are of differing amplitude.
21 In a second alternative embodiment, the two phases are of differing duration. In a third
22 alternative embodiment, the first phase is in a chopped wave form. In a fourth alternative
23 embodiment, the amplitude of the first phase is ramped. In a fifth alternative embodiment the
24 first phase is administered over 200 milliseconds after completion of a cardiac
25 beating/pumping cycle. In a preferred alternative embodiment, the first phase of stimulation
26 is an anodal pulse at maximum subthreshold amplitude for a long duration, and the second
27 phase of stimulation is a cathodal pulse of short duration and high amplitude. It is noted that
28 the aforementioned alternative embodiments can be combined in differing fashions. It is also
29 noted that these alternative embodiments are intended to be presented by way of example
30 only, and are not limiting.

Brief Description of the Drawings

Figure 1 shows a cyclic saw tooth (linear decay) stimulation-relaxation protocol for ventricular pacing.

Figure 2 shows a cyclic exponential decay stimulation-relaxation protocol for ventricular pacing.

Figure 3 is a schematic representation of leading anodal biphasic stimulation.

Figure 4 is a schematic representation of leading cathodal biphasic stimulation.

Figure 5 is a schematic representation of leading anodal stimulation of low level and long duration, followed by cathodal stimulation.

Figure 6 is a schematic representation of leading anodal stimulation of ramped low level and long duration, followed by cathodal stimulation.

Figure 7 is a schematic representation of leading anodal stimulation of low level and short duration administered in a series, followed by cathodal stimulation.

Description of the Preferred Embodiments

The fundamentals of the present invention can be understood with reference to Figures 1 and 2, which depict two cyclic stimulation-relaxation protocols for ventricular pacing, in which the maximum rate of ventricular overdrive pacing is followed by relaxation to a rate just less than the intrinsic atrial firing rate (which corresponds to ventricular escape). Figure 1 shows a cyclic saw tooth (linear decay) stimulation-relaxation protocol. Figure 2 shows a cyclic exponential decay stimulation-relaxation protocol.

Referring to Figure 1, a cyclic saw tooth stimulation-relaxation protocol for ventricular pacing is depicted with time points 102, 106, and 108 to illustrate initiation of ventricular overdrive pacing at maximum pacing rate A, followed by linear decay/relaxation of the rate of pacing to minimum pacing rate C. Each cycle has total time length 110. Intrinsic atrial firing rate B is shown as a dashed reference line. Rate difference A-B is greater than rate difference B-C in this example. During the course of linear relaxation of the ventricular pacing rate, crossover point 104 is reached when the ventricular pacing rate equals intrinsic atrial firing rate B. Thus, the period between time point 102 and crossover point 104 represents linear ventricular overdrive pacing period 112, and the period between crossover point 104 and time point 106 represents linear ventricular escape period 114. It is

1 evident that linear ventricular overdrive pacing period 112 is a longer time period than linear
2 ventricular escape period 114. Therefore, the average ventricular firing rate for this protocol,
3 with the above given relative parameters, will always be slightly greater than intrinsic atrial
4 firing rate B.

5 Referring to Figure 2, a cyclic exponential decay stimulation-relaxation ventricular
6 pacing protocol is shown with ventricular overdrive pacing to maximum pacing rate A being
7 initiated at time points 202, 206 and 208, followed by exponential relaxation of the rate of
8 pacing to minimum pacing rate C. Each cycle has total time length 210. The time course of
9 the pacing rate during the relaxation phase will be proportional to the time course of the
10 product obtained by multiplying maximum pacing rate A (or the quantity A minus a selected
11 "factor") by the proportionality $e^{1/\tau}$, where τ is the time constant. The selected "factor"
12 typically will have a value less than C. As in Figure 1, dashed line B represents the reference
13 line of intrinsic atrial firing rate. Compared to Figure 1, two parameters have been adjusted
14 in Figure 2. First, the relaxation of pacing rate is an exponential function of time instead of a
15 linear function of time. Second, minimum ventricular pacing rate C is closer to intrinsic
16 atrial firing rate B.

17 As in Figure 1, the period between time point 202 and crossover point 204 represents
18 exponential ventricular overdrive pacing period 212, and the period between crossover point
19 204 and time point 206 represents exponential ventricular escape period 214. Rate
20 difference A-B is the same in Figures 1 and 2, as are cycle lengths 110 and 210. This
21 combination of parameters produces a protocol in which exponential ventricular overdrive
22 pacing period 212 of Figure 2 is shorter than linear ventricular overdrive pacing period 112 of
23 Figure 1.

24 In the case of a curvilinear (including exponential) relaxation protocol with cycle
25 length 210, comparison of ventricular overdrive pacing period 212 and ventricular escape
26 period 214 of Figure 2 reveals that their magnitudes effectively are controlled by variations in
27 two parameters: $(A-B)/(B-C)$, and ventricular overdrive pacing period 212.

28 Referring again to Figure 1, in the case of a linear relaxation protocol with cycle
29 length 110, comparison of linear ventricular overdrive pacing period 112 and linear
30 ventricular escape period 114 reveals that their magnitudes are controlled by variation in
31 single parameter $(A-B)/(B-C)$, or any mathematical equivalent, such as $(102-104)/(104-106)$.

1
2 It is anticipated that different relaxation protocols will be required for different
3 pathologies and different medical situations. In addition, a virtually infinite array of
4 relaxation protocols are possible in theory. Thus, the preferred embodiment of the present
5 invention contemplates any monotonic relaxation protocol, where "monotonic" indicates a
6 unidirectional change in the applied ventricular pacing rate. Further, "unidirectional change"
7 is to be understood to refer to a change in ventricular pacing rate that is in the direction of
8 decreasing ventricular pacing rate, and to include periods of time in which there is no change
9 in ventricular pacing rate.

10 Therefore, the preferred embodiment of the present invention contemplates relaxation
11 protocols beyond the two depicted in Figures 1 and 2, as long as the relaxation protocol
12 embodies unidirectional change in ventricular pacing rate as defined above. Thus, the shapes
13 of the relaxation curves can generally be decreasing linear, decreasing curvilinear, decreasing
14 in an exponential fashion, include one or more periods at a constant pacing rate, or
15 combinations of these. For example, with reference to Figure 1, one can imagine a protocol
16 in which, between time points 102 and 104, there is a small time segment over which the
17 voltage is constant, followed by linear relaxation at the same or a different rate of relaxation
18 (i.e., the same or a different slope) compared to the initial rate of relaxation. In one
19 embodiment, the same or different rate of relaxation that follows the brief period of constant
20 voltage is maintained up to time point 106, which marks the end of one cycle and the
21 beginning of the next cycle.

22 Alternate embodiments encompass relaxation protocols in which ventricular pacing
23 rates are not monotonic; i.e., as the ventricular pacing rate is declining in a given cycle, time
24 periods in which the ventricular pacing rates are increased slightly can be included. Further
25 alternative embodiments can include the use of combinations of different rates of relaxation
26 within a single cycle, for example, within time segment 102 - 106, or 202 - 206.

27 Typically, physiological data from one or more sensing electrodes (including
28 electrodes that perform both pacing and sensing) are used to determine whether an "action
29 criterion" has been met, in order to initiate a cyclic pacing protocol if the situation so
30 demands. Such sensing may be directed to detecting such nonlimiting physiological
31 parameters as abnormal or unacceptably long A-V delays, whether atrial firing entrains both

1 left and right ventricles, length of the QRS complex, magnitude of the QRS complex, heart
2 rate, arterial and/or venous blood pressure, ventricular fibrillation, atrial fibrillation, and
3 probability density function ("PDF"). At the end of such a cyclic pacing protocol, sensing
4 again is performed to determine if additional pacing is required. Alternatively, sensing can be
5 conducted concurrently with a cyclic pacing protocol.

6 The ventricular firing protocol is activated upon detection of a QRS complex, and is
7 set at an overdrive rate of only a few beats per minute (i.e., no more than 3-5 beats per
8 minute) greater than the intrinsic atrial firing rate. Next, the ventricular firing rate is slowly
9 decreased ("relaxed") to a rate just a few beats per minute (i.e., no more than 2-3 beats per
10 minute; ideally, only 1-2 beats per minute) below the intrinsic atrial firing rate, which leads to
11 ventricular escape (i.e., atrial firing and contraction no longer coordinate perfectly with
12 ventricular firing and contraction). Heart rates could vary from about 40 to 120 beats per
13 minute, with these rates being largely determined by the intrinsic physiology of the heart.
14 Rates that vary greatly from this 40 to 120 beats per minute range would not be beneficial
15 physiologically.

16 What is central to the present invention is that the ventricular pacing rates hover not
17 far from the intrinsic atrial firing rate so as to minimize the energy requirements of the
18 myocardium. Generally, practice of the present invention will result in an average ventricular
19 beating rate that is just slightly greater than the intrinsic atrial firing rate. However, it is
20 anticipated that some pathological/medical conditions will minimize the cardiac energy
21 requirements with a relaxation protocol that results in an average ventricular beating rate that
22 is equal to, or just slightly less than, the intrinsic atrial firing rate; and such relaxation
23 protocols are well within the scope of the present invention.

24 The application of cyclic ventricular pacing with any of the above range of relaxation
25 protocols pertains not only to mono-ventricular pacing, but also to biventricular pacing,
26 and/or pacing from multiple sites. In the case of biventricular pacing, right and left ventricles
27 can be cyclically paced either on the same or similar time protocol or independently of one
28 another. Furthermore, one pacing electrode or multiple pacing electrodes can be employed
29 per ventricle, and the pacing electrodes can be applied to the external surfaces of the
30 ventricles and/or to the internal surfaces. Typically, internal pacing electrodes will be applied
31 via the vena cava and the right atrium to the right ventricle only; however, multiple internal

1 pacing electrodes are also contemplated for the left ventricle.

2 Additional embodiments encompass the use of monophasic stimulation, as well as
3 biphasic stimulation. Furthermore, the monophasic stimulation and the biphasic stimulation
4 can be applied to either atria or ventricles. Monophasic stimulation can be either cathodal or
5 anodal, and is known to those skilled in the art. Biphasic cardiac stimulation is disclosed in
6 United States Patent Application No. 08/699,552 to Mower, which is hereby incorporated by
7 reference in its entirety.

8 Typically, a cyclic pacing/relaxation period will fall within the three to 30 second
9 range; however, longer periods also are contemplated, particularly for patients with more
10 "difficult" pathologies.

11 Figure 3 depicts biphasic electrical stimulation wherein a first stimulation phase,
12 comprising anodal stimulus 302, is administered having amplitude 304 and duration 306.
13 This first stimulation phase is immediately followed by a second stimulation phase
14 comprising cathodal stimulation 308 of equal intensity and duration.

15 Figure 4 depicts biphasic electrical stimulation wherein a first stimulation phase,
16 comprising cathodal stimulation 402 having amplitude 404 and duration 406, is administered.
17 This first stimulation phase is immediately followed by a second stimulation phase
18 comprising anodal stimulation 408 of equal intensity and duration.

19 Figure 5 depicts a preferred embodiment of biphasic stimulation wherein a first
20 stimulation phase, comprising low level, long duration anodal stimulation 502 having
21 amplitude 504 and duration 506, is administered. This first stimulation phase is immediately
22 followed by a second stimulation phase comprising cathodal stimulation 508 of conventional
23 intensity and duration. In differing alternative embodiments, anodal stimulation 502 is: 1) at
24 maximum subthreshold amplitude; 2) less than three volts; 3) of a duration of
25 approximately two to eight milliseconds; and/or 4) administered over 200 milliseconds post
26 heart beat. Maximum subthreshold amplitude is understood to mean the maximum
27 stimulation amplitude that can be administered without eliciting a contraction. In differing
28 alternative embodiments, cathodal stimulation 508 is: 1) of a short duration; 2)
29 approximately 0.3 to 1.5 milliseconds; 3) of a high amplitude; 4) in the approximate range
30 of three to twenty volts; and/or 5) of a duration less than 0.3 millisecond and at a voltage
31 greater than twenty volts. In a preferred embodiment, cathodal stimulation is about 0.8

1 millisecond. In the manner disclosed by these embodiments, as well as those alterations and
2 modifications which can become obvious upon the reading of this specification, a maximum
3 membrane potential without activation is achieved in the first phase of stimulation.

4 Figure 6 depicts an alternative preferred embodiment of biphasic stimulation wherein
5 a first stimulation phase, comprising anodal stimulation 602, is administered over period 604
6 with rising intensity level 606. The ramp of rising intensity level 606 can be linear or non-
7 linear, and the slope can vary. This anodal stimulation is immediately followed by a second
8 stimulation phase comprising cathodal stimulation 608 of conventional intensity and
9 duration. In alternative embodiments, anodal stimulation 602: (1) rises to a maximum
10 subthreshold amplitude less than three volts; (2) is of a duration of approximately two to eight
11 milliseconds; and/or (3) is administered over 200 milliseconds post heart beat. In yet other
12 alternative embodiments, cathodal stimulation 608 is: (1) of a short duration; (2)
13 approximately 0.3 to 1.5 milliseconds; (3) of a high amplitude; (4) in the approximate range
14 of three to twenty volts; and/or (5) of a duration less than 0.3 milliseconds and at a voltage
15 greater than twenty volts. In the manner disclosed by these embodiments, as well as those
16 alterations and modifications which can become obvious upon the reading of this
17 specification, a maximum membrane potential without activation is achieved in the first
18 phase of stimulation.

19 Figure 7 depicts biphasic electrical stimulation wherein a first stimulation phase,
20 comprising series 702 of anodal pulses, is administered at amplitude 704. In one
21 embodiment, rest period 706 is of equal duration to stimulation period 708, and is
22 administered at baseline amplitude. In an alternative embodiment, rest period 706 is of a
23 differing duration than stimulation period 708, and is administered at baseline amplitude.
24 Rest period 706 occurs after each stimulation period 708, with the exception that a second
25 stimulation phase, comprising cathodal stimulation 710 of conventional intensity and
26 duration, immediately follows the completion of series 702. In alternative embodiments: (1)
27 the total charge transferred through series 702 of anodal stimulation is at the maximum
28 subthreshold level; and/or (2) the first stimulation pulse of series 702 is administered over
29 200 milliseconds post heart beat. In yet other alternative embodiments, cathodal stimulation
30 710 is: (1) of a short duration; (2) approximately 0.3 to 1.5 milliseconds; (3) of a high
31 amplitude; (4) in the approximate range of three to twenty volts, and/or (5) of a duration less

1 than 0.3 milliseconds and at a voltage greater than twenty volts.

2 The preferred practice of the present invention is directed to ventricular pacing where
3 the pacing rate skirts just above and below the intrinsic atrial pacing rate, and is timed (albeit
4 indirectly) relative to intrinsic atrial firing in order to achieve optimal coordinated cardiac
5 function. However, situations can be anticipated in which ventricular pacing is effected
6 independently of intrinsic atrial firing.

7 Furthermore, when atrial rhythmicity is pathologic, the present invention can be
8 practiced with respect to the rhythmicity of pacemaker paced atria. In embodiments in which
9 atria are paced by extrinsic pacemakers, the clinical practitioner first sets the rate of atrial
10 pacing, which can be fixed, or can be variable to permit appropriate response to changes in
11 physical activity or other change which would require a change in heart rate, for example, an
12 increased heart rate during a period of fever. Second, the ventricular firing protocol is
13 selected according to the principles described and disclosed herein. It is to be emphasized
14 that selection of the ventricular firing protocol generally will be a decision that is made
15 independently of the atrial beating pattern, whether the atrial beating pattern is set
16 intrinsically or extrinsically, for example, by a pacemaker. However, it is within the scope of
17 the present invention to apply the teachings herein to cases in which decisions regarding
18 extrinsically controlled atrial and ventricular beating protocols are considered in a linked,
19 integrated manner.

20 In addition, testing procedures can be applied to achieve optimal parameters for a
21 given patient with a particular constellation of pathologies. Thus, it is within the scope of the
22 present invention to test, and vary, alternative stimulation pulse waveforms, for example,
23 durations, amplitudes, and shapes of the various waveforms required to reach optimal
24 physiological parameters for a particular patient at a given time. Further, various measurable
25 parameters may be used to assess the effects of changes in stimulus waveforms, for example,
26 the effects on pulse pressure, duration of the QRS complex, maximum fusion, and production
27 of a minimal intrinsic heart rate, to name but a few.

28 Having thus described the basic concept of the invention, it will be readily apparent to
29 those skilled in the art that the foregoing detailed disclosure is intended to be presented by
30 way of example only, and is not limiting. Various alterations, improvements and
31 modifications will occur and are intended to those skilled in the art, but are not expressly

- 1 stated herein. These modifications, alterations and improvements are intended to be
- 2 suggested hereby, and within the scope of the invention. Accordingly, the invention is
- 3 limited only by the following claims and equivalents thereto.

1 **Claims**

2 1. A method for cardiac pacing for a heart having an intrinsic atrial firing rate,
3 comprising:

4 applying a series of pacing stimuli to at least one ventricle having an initial pacing
5 rate,

6 where the initial pacing rate is slightly greater than the intrinsic atrial firing
7 rate;

8 and

9 decreasing the pacing rate over time from the initial pacing rate to a minimum pacing
10 rate that is slightly less than the intrinsic atrial firing rate.

11 2. The method for cardiac pacing according to claim 1, further comprising
12 sensing

13 physiological parameters to determine if additional cardiac pacing is needed.

14 3. The method for cardiac pacing according to claim 2, where the physiological
15 parameters are selected from the group consisting of A-V interval, atrial entrainment of left
16 and right ventricles, length of QRS complex, magnitude of QRS complex, arterial blood
17 pressure, venous blood pressure, heart rate, ventricular fibrillation, atrial fibrillation, and
18 probability density function.

19 4. The method for cardiac pacing according to claim 1, where applying the
20 pacing

21 stimuli and decreasing the pacing rate is repeated in a cyclic pattern.

22 5. The method for cardiac pacing according to claim 1, where a protocol for
23 decreasing the pacing rate over time is selected from the group consisting of linear,
24 curvilinear, exponential, and combinations thereof.

25 6. The method for cardiac pacing according to claim 5, where the protocol for
26 decreasing the pacing rate includes one or more periods of time in which the pacing rate is
27 held constant.

28 7. The method for cardiac pacing according to claim 1, where a protocol for
29 decreasing the pacing rate includes one or more periods of time in which the pacing rate is
30 held constant.

31 8. The method for cardiac pacing according to claim 1, where the initial pacing

- 1 rate
2 minus the intrinsic atrial firing rate is greater than the intrinsic atrial firing rate minus the
3 minimum pacing rate.
- 4 9. The method for cardiac pacing according to claim 1, where the initial pacing
5 rate
6 minus the intrinsic atrial firing rate is equal to the intrinsic atrial firing rate minus the
7 minimum pacing rate.
- 8 10. The method for cardiac pacing according to claim 1, where the initial pacing
9 rate
10 minus the intrinsic atrial firing rate is less than the intrinsic atrial firing rate minus the
11 minimum pacing rate.
- 12 11. The method for cardiac pacing according to claim 1, where the pacing stimuli
13 are
14 selected from the group consisting of monophasic stimulation and biphasic stimulation.
- 15 12. The method for cardiac pacing according to claim 11, where the monophasic
16 stimulation is selected from the group consisting of cathodal stimulation and anodal
17 stimulation.
- 18 13. The method for cardiac pacing according to claim 11, where the biphasic
19 stimulation comprises an anodal stimulation phase followed by a cathodal stimulation phase.
- 20 14. The method for cardiac pacing according to claim 13, where the anodal
21 stimulation phase:
22 has a magnitude equal to or less than a maximum subthreshold amplitude; and
23 has an approximate shape selected from the group consisting of square wave,
24 increasing ramp, and series of short duration square waves.
- 25 15. The method for cardiac pacing according to claim 1, where the pacing stimuli
26 are
27 applied via multiple electrodes to at least one ventricle.
- 28 16. A method for cardiac pacing for a heart with a paced atrial firing rate,
29 comprising:
30 applying a series of pacing stimuli to at least one ventricle, where the initial
31 ventricular pacing rate is slightly greater than the paced atrial firing rate; and

1 decreasing the initial ventricular pacing rate over time to a minimum pacing rate that
2 is slightly less than the paced atrial firing rate.

3 17. The method for cardiac pacing according to claim 16, wherein applying the
4 pacing

5 stimuli and decreasing the pacing rate is repeated in a cyclic pattern.

6 18. The method for cardiac pacing according to claim 16, where a protocol for
7 decreasing the initial ventricular pacing rate over time is selected from the group consisting of
8 linear, curvilinear, exponential, and combinations thereof.

9 19. The method for cardiac pacing according to claim 18, where the protocol for
10 decreasing the initial pacing rate includes one or more periods of time in which the pacing
11 rate is held constant.

12 20. The method for cardiac pacing according to claim 16, where a protocol for
13 decreasing the pacing rate includes one or more periods of time in which the pacing rate is
14 held constant.

15 21. The method for cardiac pacing according to claim 16, where the initial
16 ventricular
17 pacing rate minus the paced atrial firing rate is greater than the paced atrial firing rate minus
18 the minimum ventricular pacing rate.

19 22. The method for cardiac pacing according to claim 16, where the initial
20 ventricular
21 pacing rate minus the paced atrial firing rate is equal to the paced atrial firing rate minus the
22 minimum ventricular pacing rate.

23 23. The method for cardiac pacing according to claim 16, where the initial
24 ventricular
25 pacing rate minus the paced atrial firing rate is less than the paced atrial firing rate minus the
26 minimum ventricular pacing rate.

27 24. The method for cardiac pacing according to claim 16, where the pacing stimuli
28 are
29 selected from the group consisting of monophasic stimulation and biphasic stimulation.

30 25. The method for cardiac pacing according to claim 24, where the monophasic
31 stimulation is selected from the group consisting of cathodal stimulation and anodal

1 stimulation.

2 26. The method for cardiac pacing according to claim 24, where the biphasic
3 stimulation comprises an anodal stimulation phase followed by a cathodal stimulation phase.

4 27. The method for cardiac pacing according to claim 26, where the anodal
5 stimulation phase:

6 has a magnitude equal to or less than a maximum subthreshold amplitude; and

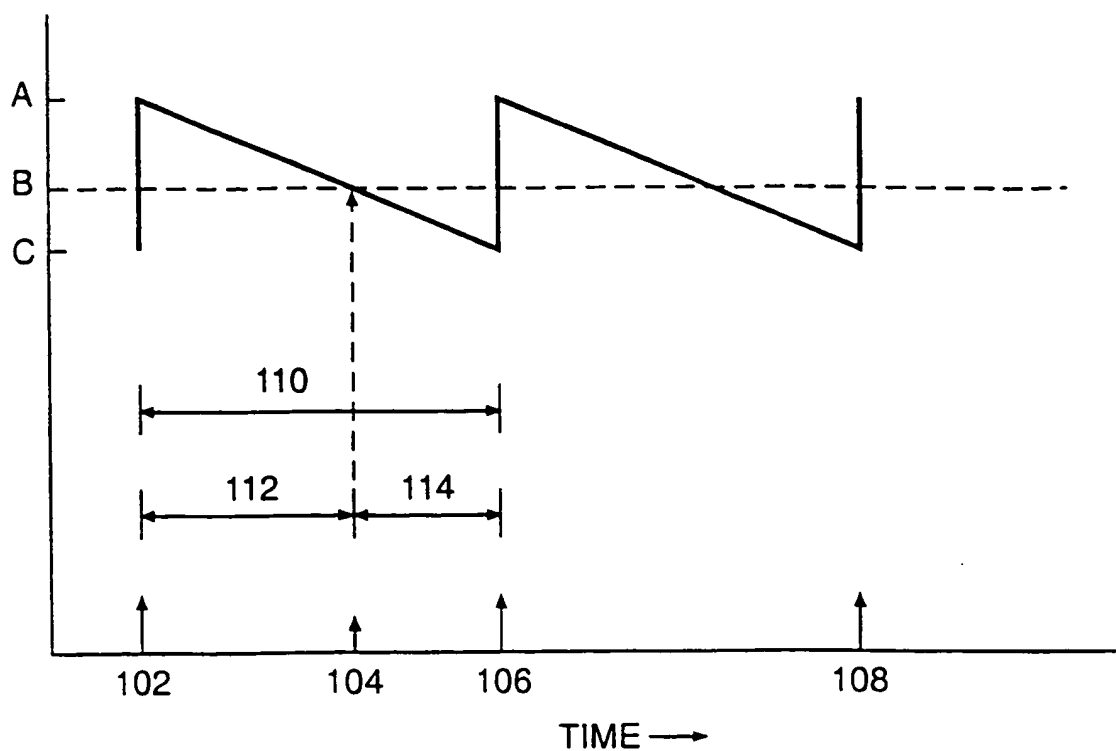
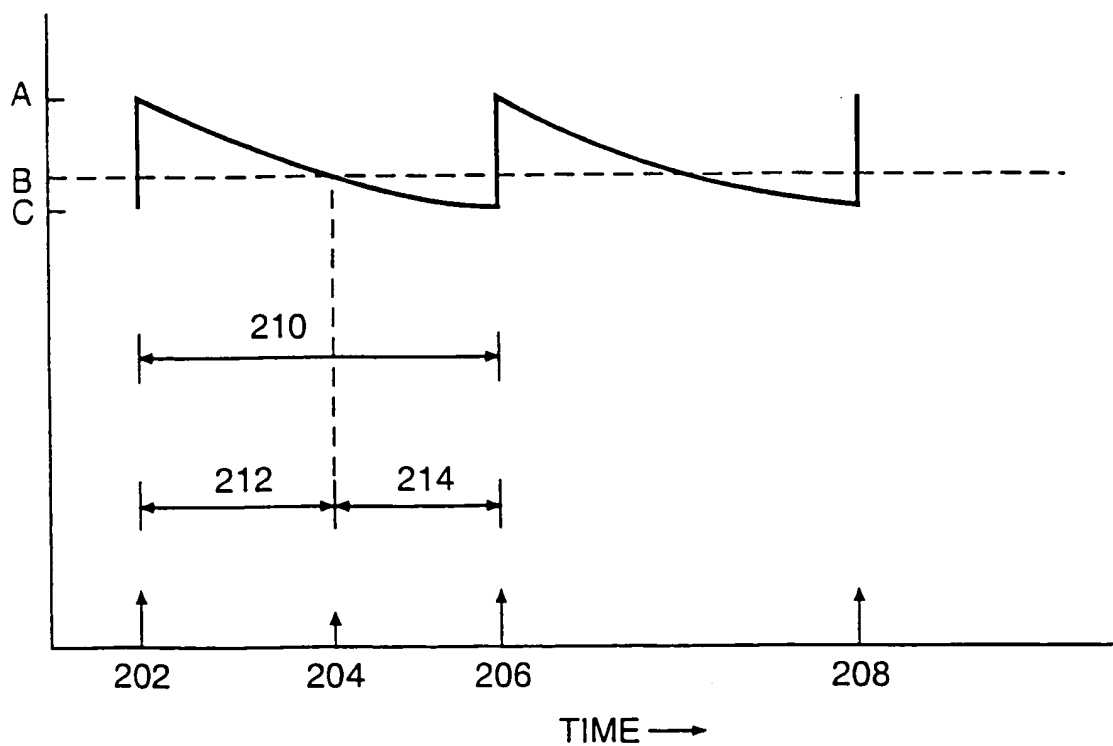
7 has an approximate shape selected from the group consisting of square wave,

8 increasing ramp, and series of short duration square waves.

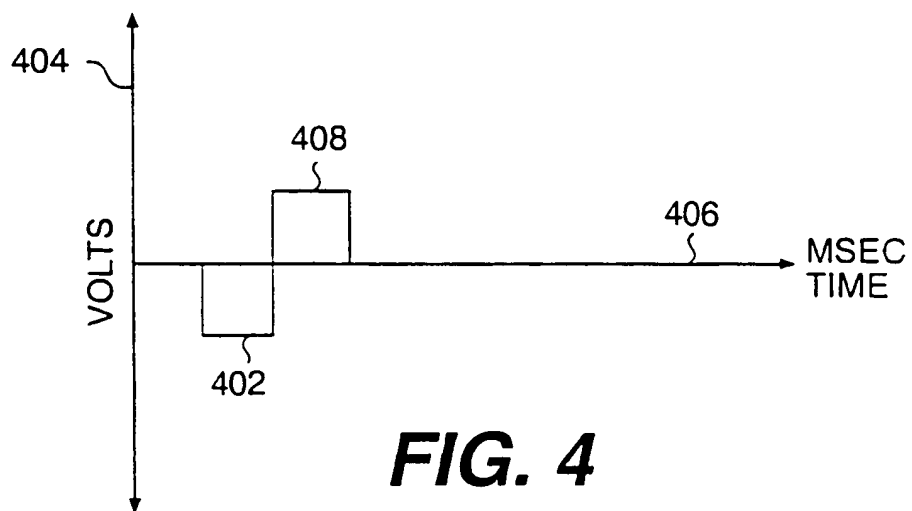
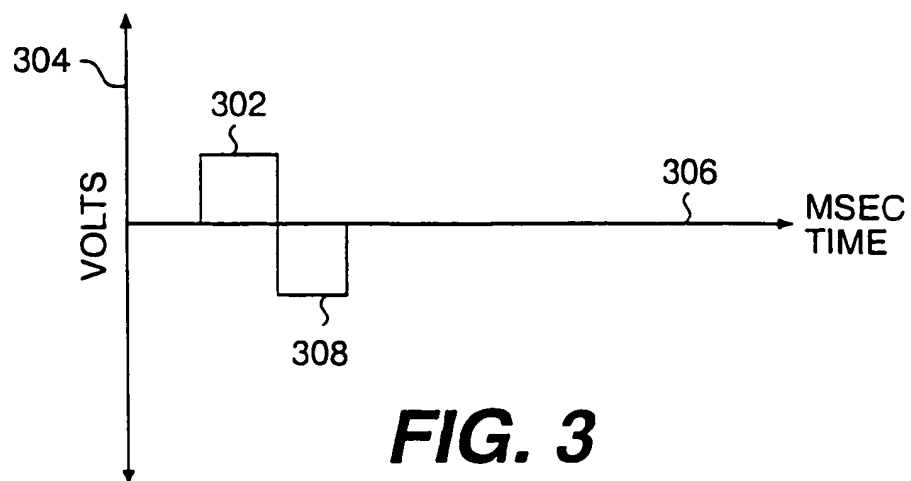
9 28. The method for cardiac pacing according to claim 16, where the pacing stimuli
10 are

11 applied via multiple electrodes to at least one ventricle.

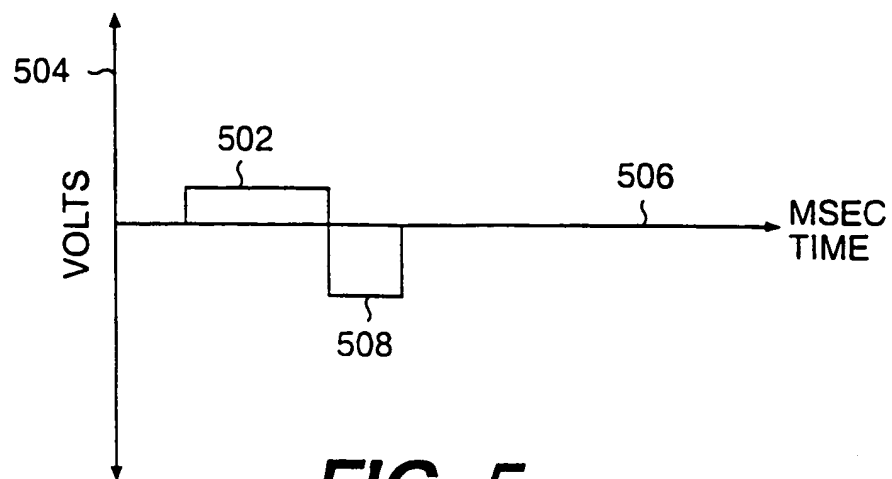
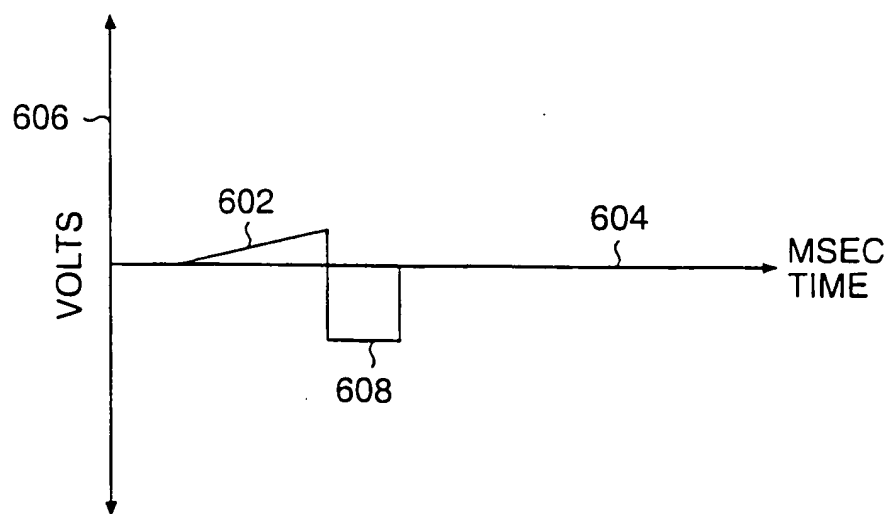
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**FIG. 1****FIG. 2**

2 / 4



3 / 4

**FIG. 5****FIG. 6**

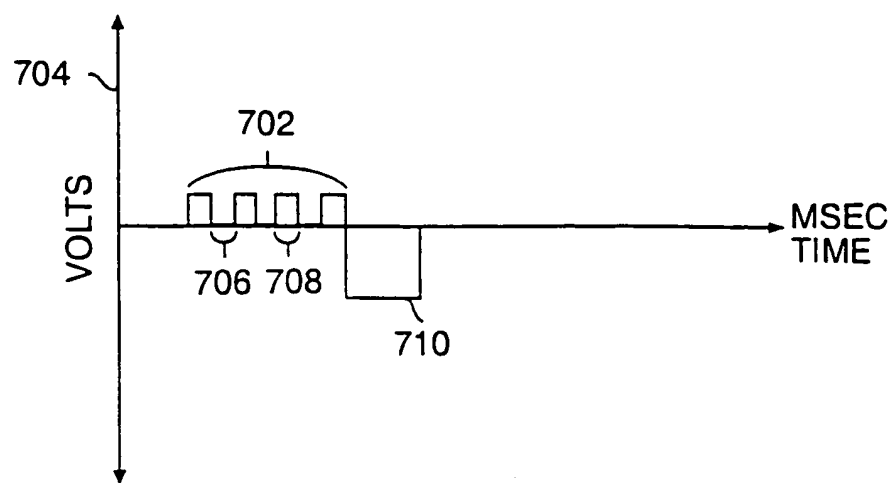


FIG. 7

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11375

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61N1/368

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 480 413 A (GREENHUT SAUL ET AL) 2 January 1996 (1996-01-02) cited in the application ---	
A	EP 0 600 631 A (SIEMENS AG) 8 June 1994 (1994-06-08) cited in the application ---	
P,A	US 5 871 506 A (MOWER MORTON M) 16 February 1999 (1999-02-16) cited in the application ---	
A	US 5 713 929 A (MEADOR JOHN T ET AL) 3 February 1998 (1998-02-03) ---	
P,A	FR 2 763 247 A (ELA MEDICAL SA) 20 November 1998 (1998-11-20) -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 August 1999

Date of mailing of the international search report

03/09/1999

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Allen, E

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 11375

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-28
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 99 /11375

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although the claims are directed to a method of treatment of the human/ animal body, the search has been carried out and based on a device to carry out the method of claims 1 and 16.

Continuation of Box I.1

Claims Nos.: 1-28

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/11375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 5713929 A	03-02-1998	AU 2996497 A EP 0902709 A WO 9741922 A	26-11-1997 24-03-1999 13-11-1997
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